ABSTRACT

Background: Adequate treatment and follow-up of a patient with nonmelanoma skin cancer is of utmost concern for a clinician. However, there is a lack of international consensus on recommendations for surgical excision margins. Furthermore, lack of familiarity of the published guidelines leads to a variety in practice styles. **Objective:** To compare the consistency in global recommendations for surgical excision margins for basal cell carcinoma, cutaneous squamous cell carcinoma, dermatofibrosarcoma protuberans, and Merkel cell carcinoma. **Methods:** A review of the current literature and global guidelines for surgical excision margins for basal cell carcinoma, cutaneous squamous cell carcinoma, dermatofibrosarcoma protuberans, and Merkel cell carcinoma. **Results:** Upon review of international guidelines, variations do exist among guidelines for peripheral and deep surgical margins. Guideline recommendations were found to be more globally consistent in margin selection for low-risk basal cell carcinoma and low-risk cutaneous squamous cell carcinoma, however, least consistent when concerning

[Abstract continued on next page]

REVIEW

A Review of the Global Guidelines on Surgical Margins for Nonmelanoma Skin Cancers

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Nonmelanoma skin cancers (NMSC) tend to lie in the shadow of melanoma, despite being more common and resulting in a higher economic burden. A recently published article revealed that from 2007 to 2011, the average annual total treatment costs were $4.8 billion for NMSC and $3.3 billion for melanoma.[1] Proper NMSC management remains as important since local invasion, delay of diagnosis, and metastasis contribute to increased cost and morbidity. Several surgical treatment options exist for NMSC and remain the standard of care. The most widely used surgical excision modalities include standard excision (SE) with postoperative margin assessment, wide local excision (WLE), and Mohs micrographic surgery (MMS), including variations of MMS. The Appropriate Use Criteria for MMS is an additional resource that can facilitate decision-making, as it factors in the affected area of the body (Area H, Area M, Area L), noteworthy patient characteristics (immunocompromised states, history

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[Abstract continued]

margin selection for dermatofibrosarcoma protuberans and Merkel cell carcinoma. **Conclusion:** Although guidelines exist, there is a need for international collaboration and consensus to determine a more unified and evidence-based approach to surgical excision as a treatment for nonmelanoma skin cancer.

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of genetic syndromes), and key tumor characteristics predictive of future recurrence.[2]

While many surgical and oncological organizations have established guidelines for the treatment of NMSC, great variations exist between the societies. Developing a collaborative consensus between organizations can help alleviate mounting frustration associated with these common cancers. This article provides a comprehensive global review of the current guidelines on surgical excision margins for basal cell carcinoma (BCC), cutaneous squamous cell carcinoma (cSCC), dermatofibrosarcoma protuberans (DFSP), and Merkel cell carcinoma (MCC).

DISCUSSION

Basal cell carcinoma. BCC and cSCC are recognized as the most common malignant skin cancer worldwide. Of the estimated 5.4 million BCC and cSCC diagnosed each year, approximately 80 percent are BCC.[2] Sun exposure is a well-established, leading risk factor, with 85 percent of BCC lesions affecting sun-exposed areas and the nose accounting for approximately 25 to 30 percent.[3]

Micronodular, infiltrative, and morpheaform patterns have greater tendencies toward aggressive behavior. Collectively, however, among the BCC subtypes, the risk of metastasis is low.[3] Primary lesions in the head and neck have greater tendencies toward recurrence, while those affecting the ears, genitalia, and other mucosal surfaces carry higher risk of metastasis. Early recognition is key in preventing onset of advanced disease.[4]

National Comprehensive Cancer Network. The National Comprehensive Cancer Network (NCCN) guidelines on surgical margin selection of BCC are categorized as low and high risk, based on risk of recurrence. Low-risk BCC describes primary lesions with well-defined borders, less than 20mm in Area L, less than 10mm in Area M, less than 6mm in Area H, and of the nodular or superficial subtype (Table 1). High-risk lesions include those that are recurrent, have poorly defined margins, are greater than or equal to 20mm in Area L, greater than or equal to 10mm in Area M, or greater than or equal to 6mm in Area H. This includes more aggressive patterns, such as morpheaform, basosquamous, sclerosing, mixed infiltrative, or micronodular subtypes. Hosts with history of immunosuppression and/or radiation, as well as those with existing perineural or bone involvement, are additionally considered high risk.[3]

NCCN recommendations stem from a large study by Wolf and Zitelli involving 117 cases of BCCs which were either less than or greater than 2cm in diameter and excised via a MMS approach.[4,5] For BCCs less than 2cm, complete removal of the lesion was achieved in 95 percent of cases via SE with 4mm peripheral surgical margins.[4,5] For BCCs greater than 2cm, margins greater than 4mm are recommended. Alternatively, MMS is considered first-line treatment in high-risk BCCs.[4] Per the NCCN, biopsy should target a depth to the deep reticular dermis if there is concern for local invasion, though deep margin recommendations during excision are not specified.[4]

Table 1. Body areas[2]

AREA H	AREA M	AREA L
"Mask areas" of the face Central face Eyelids, including inner/outer canthi Nose, chin, temple Lips, including cutaneous, mucosal, and vermillion surfaces Ears, including periauricular skin/sulci	**Cheeks**	**Trunk**
Hands, ankles, feet	**Forehead**	**Extremities** Excluding pretibial area, hands, feet, ankles, and nail units
Nail units	**Jawline**	
Nipples, areola	**Neck**	
Genitalia, including perineal and perianal areas	**Scalp**	
	Pretibial area	

European Dermatology Forum. The European Dermatology Forum (EDF) guidelines on surgical excision margins of BCC represent a compilation of recommendations based on the British Association of Dermatology guidelines (BAD), French guidelines, and previous EDF guidelines.[6–8] Low-risk BCC, defined as less than 2cm in diameter, should undergo SE using 3 to 4mm peripheral margins.[9,10] For high-risk BCC, defined mainly by larger size, it is appropriate to perform SE using 5 to 10mm peripheral margins. The EDF cites that previous studies showed complete clearance in 95 percent of cases when such margins were used. MMS is an alternative surgical therapy in appropriate candidates.[9,10]

Where appropriate, deep margins should extend to the level of the fascia, perichondrium, or periosteum, especially when involving the head. For superficial BCCs or those located in areas where there is thicker skin, the deep margin need not be as deep.[9] The overall approach should be tailored to the type of BCC.[9,11]

British Association of Dermatology. According to the British Association of Dermatology (BAD) guidelines, 4 to 5mm peripheral margins are recommended using SE for low-risk BCC. The BAD guidelines reference a study by Wolf and Vitelli, which showed a complete excision rate of 95 percent using a 3.79mm surgical excision margin.[5,7] For high-risk BCC, BAD guidelines suggest greater than 5mm peripheral margins for high-risk BCCs using SE. For primary morphoeic BCC, an extended margin greater than or equal to 13 to 15mm is recommended. MMS is an alternative surgical therapy for high-risk BCC in appropriate candidates.[7] Deep margins are recommended to extend to the level of subcutaneous fat.[7]

Cancer Council Australia and Australian Cancer Network. The Cancer Council Australia and Australian Cancer Network (CCA/ACN) guidelines categorize BCC lesions as simple and complex when determining appropriate surgical excision margins. Simple BCCs are defined as small, nodular, or superficial, and not located on the central face. Complex BCCs are

Table 2. Basal cell carcinoma global guideline comparison of surgical margins[4,7,9,12,13]

ORGANIZATION	PERIPHERAL MARGINS		DEEP MARGINS
	LOW-RISK LESIONS	HIGH-RISK LESIONS	LOW- AND HIGH-RISK LESIONS
NCCN	Preferred: SE -4mm	Preferred: MMS Alternative: SE -≥4mm	Not specified
EDF	Preferred: SE -3–4mm	Preferred: SE (or MMS) -5–10mm	• Level of fascia, perichondrium, or periosteum where appropriate (especially for lesions of the head) • Less deep margins for superficial lesions or those in areas of thicker skin
BAD	Preferred: SE -4–5mm	Preferred: SE (or MMS) ->5mm -≥13–15mm (primary morphoeic BCC)	Through level of subcutaneous fat
CCA/ACN	Preferred: SE (or MMS) -2–3mm	Preferred: SE (or MMS) -3–5mm	To include level of subcutaneous fat
Sweden	Preferred: SE -≥3–4mm	Preferred: SE -≥5mm	Not specified

British Association of Dermatology (BAD), Cancer Council Australia and Australian Cancer Network (CCA/ACN), European Dermatology Forum (EDF), National Cancer Care Network (NCCN), Mohs micrographic surgery (MMS), standard excision (SE)

defined as complex secondary to anatomic location, histologic subtype, or ill-defined nature. The CCA/ACN advise use of 2 to 3mm peripheral margins for simple BCCs and 3 to 5mm for complex BCCs using SE. The deep margin is recommended to include subcutaneous fat.[12]

Swedish guidelines. The Swedish guidelines, endorsed by the Section for Dermatologic Surgery and Oncology and the Swedish Society for Dermatology and Venereology, have also composed peripheral margin recommendations for the surgical excision of BCC. For small BCCs (not clearly defined), a minimum peripheral margin of 3 to 4mm via SE is advised. For highly aggressive BCCs, such as micronodular, metatypic, and recurrent types, a minimum peripheral margin of 5mm via SE is recommended (Table 2).[13]

Cutaneous squamous cell carcinoma. cSCC is the second most common skin cancer worldwide, with incidence rates highest in the lower latitudes. A well-established relationship exists between cSCC and ultraviolet (UV) radiation, especially UVB. Other risk factors, such as arsenic exposure and the human papilloma virus (types 6, 11, and 16), have also been associated.[3]

In comparison to BCC, cSCC has a greater propensity for invasive behavior and metastasis. Risk of metastasis is greater for lesions involving the scalp, forehead, ears, nose, and lips. Undifferentiated lesions greater than 6mm thick that have proceeded to invade deeper structures, including the musculature, perichondrium, or periosteum also have an increased risk of metastasis. cSCC types derived from transformed actinic keratoses tend to exhibit less

aggressive behavior and have a lower risk of metastasis. Recurrence is common in lesions at least 4mm thick that extend to the deep dermis.[3]

National Comprehensive Cancer Network. The NCCN guidelines categorize margin selection of cSCC as low- and high-risk and recommendations are substantiated based on the findings of Brodland and Zitelli who conducted a study involving 141 cases of primary invasive cSCC lesions treated by MMS.[15] For well-defined, low-risk tumors, it was found that 4mm peripheral margins resulted in a complete excision rate of 95 percent. Their recommendation stands as 4 to 6mm peripheral margins for low-risk lesions using SE. High-risk lesions are described as those that are ill-defined, affecting the genitalia, mucosal surfaces, face, and/or neck. For high-risk lesions greater than 6mm in high-risk locations, greater than 10mm in moderate risk locations, or those penetrating to the level of subcutaneous fat on biopsy, the NCCN advises SE with greater than 6mm peripheral margins.[20,21] Upon review of the guidelines, deep margin recommendations do not appear to be available; however, the NCCN does highlight their prognostic value in diagnosis and staging.[15]

European Dermatology Forum. The latest EDF guidelines for the management of cSCC were established by a collaboration of the EDF, the European Association of Dermato-Oncology, and the European Organization of Research and Treatment of Cancer. For low-risk, well-defined cSCC less than 2cm in diameter, the EDF recommends SE using 5mm peripheral margins. Higher risk lesions include those at least 2cm in diameter with history of chronic ulceration, presence of high histological thickness greater than or equal to 6mm, subcutaneous invasion, and/or perineural invasion. High-risk locations are described as those affecting the ear, lip, scalp, or eyelid.[16,17] For such lesions, SE with 6 to 10mm peripheral margins is recommended. MMS is an alternative surgical therapy in appropriate candidates. The deep margin should extend to the hypodermis, avoiding the aponeuroses, perichondrium, and periosteum if unaffected by tumor extension.[16]

British Association of Dermatology. Per the BAD, low-risk, clinically well-defined cSCC lesions less than 2cm in diameter require SE with peripheral margins of 4mm.[16,18] Lesions greater than 2cm should undergo SE with at least 6mm peripheral margins, including those that are moderately, poorly, or undifferentiated in character, those extending to the level of subcutaneous tissue, and those affecting high-risk areas, such as the ear, lip, eyelid, or scalp.[14,19–21] MMS is an alternative surgical approach in appropriate candidates.[18]

Cancer Council Australia and Australian Cancer Network. According to the CCA/ACN guidelines, for well-differentiated cSCC lesions less than 2cm in diameter, the recommendation is SE with 4mm peripheral margins. Lesions at least 2cm in diameter require SE using up to 10mm peripheral margins. Deep margins should extend through normal adipose tissue to ensure complete removal.[12]

Swedish guidelines. For low-risk cSCC, the Swedish guidelines recommend SE using at least 4mm peripheral margins. High-risk cSCC features include, but are not limited to, poor differentiation, location involving the ear and/or scalp, and immunosuppression in the host. Such high-risk lesions are recommended to be excised using SE with a peripheral margin of at least 6mm. Alternatively, high-risk lesions can be excised via MMS in appropriate candidates (Table 3).[13]

Dermatofibrosarcoma protuberans. Dermatofibrosarcoma protuberans (DFSP) is a locally aggressive, slow-growing sarcoma known for its highly irregular tumor shape, eccentric projections, and high recurrence rate.[22,23] The most recent data estimates an incidence of 4.1 per million person-years, most commonly in African-American female patients.[23] Greater than 90 percent of DFSP lesions have a fusion gene product, which promotes persistent production of collagen.[24–26]

Due to its more aggressive nature, treatment margin selection is crucial. Studies have shown recurrence rates of 7.3 percent following WLE.[26] Areas prone to recurrence include the extremities, head, and neck, likely secondary to difficulty achieving wide margins in these areas.[26,27]

National Comprehensive Cancer

Table 3. Cutaneous squamous cell carcinoma global guideline comparison of surgical margins[12,13,15,16,18]

ORGANIZATION	PERIPHERAL MARGINS		DEEP MARGINS
	LOW-RISK LESIONS	HIGH-RISK LESIONS	LOW- AND HIGH-RISK LESIONS
NCCN	Preferred: SE -4–6mm	Preferred: SE ->6mm	Not specified
EDF	Preferred: SE -5mm	Preferred: SE (or MMS) -6–10mm	Level of hypodermis, sparing the aponeuroses, perichondrium, and periosteum if they are unaffected by tumor extension
BAD	Preferred: SE -4mm	Preferred: SE (or MMS) -≥6mm	Not specified
CCA/ACN	Preferred: SE -4mm	Preferred: SE -≤10mm	Through normal subcutaneous fat
Sweden	Preferred: SE -4mm	Preferred: SE (or MMS) -≥6mm	Not specified

British Association of Dermatology (BAD), Cancer Council Australia and Australian Cancer Network (CCA/ACN), European Dermatology Forum (EDF), National Cancer Care Network (NCCN), Mohs micrographic surgery (MMS), standard excision (SE)

Network. For the management of DFSP, the NCCN guidelines advocate that MMS, modified Mohs surgery, or traditional WLE are all appropriate methods to achieve clear histological margins. However, tumor size, location, and cosmesis are important variables to consider when deciding on the best-suited surgical therapy for the patient.[22]

The NCCN cites two systemic reviews and a retrospective study comparing MMS with WLE. The former two cited systemic reviews identified lower recurrence rates following use of MMS compared to WLE. The latter retrospective study concluded that positive margins more frequently occurred following WLE compared to MMS, though the recurrence rates were statistically similar.[22,26,29,30] The NCCN recommendation for the management of DFSP is MMS or its variants to ensure complete removal with clear margins and minimize tissue loss where possible. Alternatively, WLE can also be used, with 2 to 4cm peripheral margins and deep margins extending to the investing fascia of the muscle or pericranium where appropriate. In consideration of the eccentric projections seen with DFSP, a complete histologic assessment of all surgical margins should be completed prior to attempting reconstruction of the defect to avoid tumor seeding and subsequent spreading.[22,31,32]

European Dermatology Forum. The latest EDF guidelines on the management of DFSP were established by a collaboration of the EDF, the European Association of Dermato-Oncology, and the European Organization of Research and Treatment of Cancer. For DFSP, the EDF favors MMS over WLE. Should WLE be pursued, the EDF recommends 1 to 1.3cm peripheral margins based on findings using micrographic techniques and deep margins extending to the deep fascia. For DFSP with fibrosarcomatous change, WLE or MMS can be

Table 4. Dermatofibrosarcoma protuberans global guideline comparison of surgical margins[22,33–35]

ORGANIZATION	PERIPHERAL MARGINS	DEEP MARGINS
NCCN	Preferred: WLE (or MMS) -2–4cm	Level of investing fascial layer
EDF	Preferred: MMS -1–1.3cm -3cm (DFSP with fibrosarcomatous change) DFSP with fibrosarcomatous change: MMS or WLE -3cm	Level of deep fascia
BAD	Preferred: MMS	Not specified
Denmark	Preferred: WLE (or MMS) -2–3cm	Level of deep fascia

British Association of Dermatology (BAD), dermatofibrosarcoma protuberans (DFSP), European Dermatology Forum (EDF), National Cancer Care Network (NCCN), Mohs micrographic surgery (MMS), wide local excision (WLE)

performed and an extended peripheral margin of 3cm is recommended.[33]

British Association of Dermatology. The BAD historically recommended WLE as first-line treatment for DFSP. However, in recent years, the British Society for Dermatological Surgery revised these recommendations, now instead advocating for MMS. The BAD guidelines ration that because of DFSP's subclinical and asymmetrical extension into cutaneous anatomy, MMS is preferred to ensure complete removal.[34]

Danish guidelines. For the management of DFSP, Danish guidelines recommend WLE using 2 to 3cm peripheral margins and deep margins to include the deep fascia. Alternatively, MMS can be used as a first-line treatment in appropriate candidates (Table 4).[35]

Merkel cell carcinoma. MCC is a rare neuroendocrine tumor historically known for its predominance in immunocompromised individuals. In the past two decades, the incidence has tripled in the general population. The two-year mortality of MCC is approximately 28 percent.[36–38] MCC has been associated with excess UV radiation exposure, with 81 percent of lesions located in sun-exposed areas.[39,40] The Merkel cell polyomavirus, a part of the normal human flora, accounts for approximately 80 percent of MCCs.[41,42]

Due to the asymptomatic nature, rapid expansion, and tendency for aggressiveness, clinical presentations of MCC are often delayed, resulting in metastatic disease at first presentation.[38,43]

National Comprehensive Cancer Network. According to the NCCN, WLE remains the standard of care for MCC. The current recommendation is 1 to 2cm peripheral margins and deep margins extending to the investing fascial layer of the muscle or pericranium where clinically applicable.[44,45] Sentinel lymph node biopsy (SLNB) is advised, but in lesions involving the head and neck there is decreased utility secondary to the complexity of this regional lymphatic system and tendency for false negatives. Inclusion of local adjuvant radiotherapy can be useful, but is not necessary.[44]

European Dermatology Forum. The latest EDF guidelines were established by a collaboration of the EDF, the European Association of Dermato-Oncology, and the European Organization of Research and Treatment of Cancer. Due to the tendency of these tumors to develop microscopic satellite lesions,

Table 5. Merkel cell carcinoma global guideline comparison of surgical margins[44,46–48]

ORGANIZATION	PERIPHERAL MARGINS	DEEP MARGINS
NCCN	Preferred: WLE -1–2cm Alternative: MMS (provided it does not interfere with SNLB when indicated)	Level of investing fascial layer
EDF	Preferred: MMS -1–2cm	Not specified
Denmark	Preferred: WLE -2–3cm Alternative: MMS	Level of underlying fascia
German	Preferred: WLE -3cm Alternative: MMS	Not specified

European Dermatology Forum (EDF), National Cancer Care Network (NCCN), Mohs micrographic surgery (MMS), sentinel lymph node biopsy (SNLB), wide local excision (WLE)

microscopically controlled surgery is preferred for excision of MCC using a peripheral excision margin of 1 to 2cm. SLNB is recommended as well as local radiotherapy.[46]

Danish guidelines. For the management of MCC, the Danish guidelines recommend WLE as first-line treatment. Peripheral margins of 2 to 3cm are advised, as well as deep margins extending to the level of the deep fascia. MMS can be used alternatively if such surgical margins cannot be obtained. SLNB is advised to assist with tumor staging, chest x-ray to exclude the diagnosis of lung cancer, positron emission tomography (preferred) or computerized tomography of the chest and abdomen to rule out metastasis, and local adjuvant radiotherapy as a final measure to assist with curative treatment.[47]

Short German guidelines. According to the Short German guidelines, WLE is preferred as first-line treatment for MCC. Peripheral margins of 3cm are recommended, secondary to this tumor's high risk of recurrence. If such margins cannot be obtained, MMS is advised. Also recommended are SLNB and radiotherapy to target the tumor and regional lymph nodes. Adjuvant chemotherapy can be used for palliative measures (Table 5).[48]

CONCLUSION

After thorough review of international guidelines, it is clear that variations exist among the medical societies. Although some organizations share similar guidelines for certain portions of NMSC management, there is a lack of consistency evident on direct comparison. The least consistency was noted for DFSP and MCC peripheral margin recommendations. In contrast, great consistency was evident for low-risk BCC and cSCC peripheral margin recommendations. Ample global recommendations are available for excision of BCC and cSCC in comparison to DFSP and MCC, likely attributable to a lack of patients available for clinical trials and chart review.

Future research should be directed at creating unified, global guidelines for peripheral and deep surgical margins for these NMSCs, especially for the more aggressive histological subtypes. Finally, the guidelines are centered on evidence-based medicine and are meant to serve as a "guide." They should never replace clinical judgment to ensure delivery of the highest quality of patient care and best clinical outcomes.

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